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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

6

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/729,454	Applicant(s) LASEK ET AL.	
	Examiner Natalie A. Davis	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment of claim 3 and election with traverse of Group I, claims 1-8, species SEQ ID NO: 1 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the invention of Group I encompasses the claims of Groups II-V and could be examined at the same time, the members of the Markush group are few and closely related and may be examined without a serious burden. This is not found persuasive because an independent search of each fragment and variant would require a search of 26 different sequences, which are structurally and functionally different.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-2 and 4-8 are being examined as belonging to the elected Group I, species SEQ ID NO: 1, while claims 3, and 9-20 are withdrawn from examination as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement received 23 February 2001 has been considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1(e) and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1(e) recites "biologically active" portion. The disclosure does not teach the metes and bounds for activity, which is biological that is to be used as a measure for determining what cDNA portion is encompassed by " biologically active ." The claims are indefinite since the metes and bounds of the claimed invention cannot be ascertained.

b. Claim 5 recites "substrate." It is not clear as to what substrate comprises the claimed cDNA.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim1-2 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.,1988). They include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The elected claims are drawn to an isolated mammalian cDNA or a fragment thereof or a portion thereof encoding a protein having the amino acid sequence of SEQ ID NO:1, further drawn to an isolated mammalian cDNA encoding a protein of SEQ ID NO:1, a composition comprising the cDNA of claim 1 or the complement thereof, a substrate comprising the cDNA of claim 1 or a complement thereof, a probe comprising the cDNA of claim 1 or a complement thereof, a vector comprising the cDNA of claim 1, and a host cell comprising the vector of claim. 7.

The specification discloses that the claimed invention is an isolated mammalian cDNA, which encodes a mammalian intestinal protein (SEQ ID NO: 1), which may be used to diagnose colon cancer disorders and as a probe in hybridization assays (page 4). The disclosure shows the differential expression of SEQ ID NO:1 in tissues of patients with colon disorders relative to normal colon tissue (Table 5, page 47). Furthermore, the cDNA may be used in chromosome

mapping (page 33), hybridization technology and analysis, (page 34), and may be used on micro arrays (page 38).

5. The instant disclosure fails to meet the enablement requirement for the following reasons:

The specification discloses that the claimed cDNA may be used to diagnose colon cancer shows differential expression in colon cancers tissue versus normal colon tissue. Since there is no evidence in the art or in the specification teaching SEQ ID NO: 1 expression levels and its correlation with colon cancer, it would be unpredictable to use it to diagnose cancer based on SEQ ID NO: 1 expression. Furthermore, in order for the claimed invention to be used to diagnose colon cancer it must be certain that changes in the expression levels of SEQ ID NO: 1 in a normal biological sample as compared to levels in a cancerous biological sample is indicative of a cancer and not some other disease. This would require the experimentation of numerous biological samples. Furthermore, it would require undue experimentation to one of ordinary skill in the art to make an antigenic epitope, oligopeptide, biologically active portion of SEQ ID NO:1 or 2 because there is no guidance as to which regions of the cDNA may be used to make an epitope or oligopeptide that will function as contemplated. One of ordinary skill in the art would not know how to make or select for the biologically active portion of SEQ ID NO:1 or 2 because the specification does not define what activity is biological or what regions of the invention are resopsonsible for claimed activity.

6. The specification discloses the differential expression of SEQ ID NO: 1 in colon cancer tissue versus normal colon tissue (Table 5, page 47) using micro array analysis, but does not provide guidance as to what level of expression would constitute abnormal levels and how these levels would be indicative of colon cancer. The disclosure only shows the detection of SEQ ID NO: 1 expression in known cancers and does not give any definitive evidence of cancer diagnosis. Accordingly, one of ordinary skill in the art would be required to perform undue experimentation in order to practice the invention as claimed.

7. Lehninger, et al. (Principles of Biochemistry, 2nd Ed., Worth Publishers, NY, 1993) is cited in order to establish the general state of the art and the level of predictability of hybridization. Lehninger, et al. teach that hybridization requires the pairing of nucleotide bases of two nucleic acid strands which are complementary (p. 343) and teaches that complementary strands are not identical in either base pair sequence or composition, that is wherever adenine

appears in one chain, thymidine is found in the other and wherever guanine appears in one chain, cytosine is found in the other (p. 335). Applicant has not taught how to hybridize identical nucleic acid strands, one to the other and in view in the teaching of Lehninger, et al. one of ordinary skill in the art would not clearly expect to be able to hybridize two identical nucleic acid strands one to the other. Applicant has not taught how to hybridize identical nucleic acid strands or for example, mRNA that was derived from cDNA to the complement of that cDNA strand, one to the other. In view of the Lehninger, et al. teaching, one of ordinary skill in the art would not clearly expect to be able to hybridize two identical nucleic acid strands one to the other.

8. The specification indicates that a variant refers to a molecule that are recognized variations of a cDNA or a protein encoded by a cDNA, which may include splice and allelic variants. Other variants include single nucleotide polymorphisims (SNP), which may have additions, deletions, or substitutions with conservatice or non-conservative substitutions, which may or may not result in a change in the amino acid it encodes or its structure. There are many nucleic acid molecules that may or may not perform the same biological functions and the specification does not give any guidance to which molecules having at least 80% sequence identity to SEQ ID NO: 1 will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity, as biological activity is not taught and thus, must be preserved so the molecule will function as claimed. Thus, it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any nucleic acid molecule that is at least 80% identical to SEQ ID NO: 1 and applicant has not enabled all of these types of modifications because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed.

9. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid

sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Therefore, in view of the lack of predictability of the prior art and the absence of working examples and insufficient guidance to screen for the biological activities as claimed, it would require undue experimentation for one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1-2 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Boll, et al., (1993).

The elected claims are drawn to an isolated mammalian cDNA or a fragment thereof or a portion thereof encoding a protein having the amino acid sequence of SEQ ID NO:1, further drawn to an isolated mammalian cDNA encoding a protein of SEQ ID NO:1, a composition comprising the cDNA of claim 1 or the complement thereof, a substrate comprising the cDNA of

claim 1 or a complement thereof, a probe comprising the cDNA of claim 1 or a complement thereof, a vector comprising the cDNA of claim 1, and a host cell comprising the vector of claim.

The specification defines a portion as any part of a protein used for any purpose (p. 9). Boll, et al. discloses cDNA that encodes a portion thereof of SEQ ID NO:1, thus anticipating the invention as claimed. It is inherent that cDNA may be comprised in a composition, substrate, vector, host cell, and as a probe.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, Ph.D.
October 22, 2001

GEETHA P. BANSAL
PRIMARY EXAMINER